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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL SALT AND POLYMORPHS OF DESLORATADINE HEMIFUMARATE

(57) Abstract: This invention provides a process of preparation of novel polymorphic hemifumarate salts of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine, hereinafter called "desloratadine". These polymorphic salt forms show much higher solubility in water and also in protic organic solvents compare to the parent desloratadine. The process of preparing the polymorphic forms comprising: a) mixing the ethanolic solution of desloratadine and fumaric acid at a temperature of from about 55°C to 70°C, and stirring for 30 to 45 minutes after mixing, and thereafter filtering the solid thereby prepared in hot condition; to yield the polymorphic form 2 having a DSC of 232°C ± 2°C; or b) mixing the ethanolic solution of desloratadine and fumaric acid at a temperature of from about 15°C to room temperature (25°C) and stirring at this temperature for 30 to 45 minutes, then filtering at room temperature; to yield the polymorphic form 1 having a DSC of 224°C ± 2°C.

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NOVEL SALT AND POLYMORPHS OF DESLORATADINE HEMIFUMARATE

Field of the Invention

This invention provides a process of preparation of novel polymorphic hemifumarate salts of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine, hereinafter called "desloratadine". These polymorphic salt forms show much higher solubility in water and also in protic organic solvents compare to the parent desloratadine. In addition, formation of hemifumarate salt imparts to the desloratadine molecule a greater stability than the desloratadine itself. Desloratadine has shown great promise in the treatment as non-sedative antihistamine.

Background of the Invention

It is known that desloratadine as actually used for pharmaceutical formulation has very little or no solubility in water. Another aspect of the drug is that desloratadine is not stable and shows discoloration during stability studies. These dual characteristics of the drug require non-flexible special formulation design to prevent degradation and to retain potency. It has been found (see U.S. Patent No. 6,100,274) that in solid dosage form desloratadine, containing acidic excipients along with lactose monohydrate resulted in a large amount (14%) of decomposition after one week at 40°C and 75% relative humidity.

The present invention provides a stable novel desloratadine hemifumarate salt with high water solubility and compatibility with a wide range of excipients for pharmaceutical formulation. The process of preparation of polymorphic form of desloratadine hemifumarate salt produces consistently high quality of the active pharmaceutical ingredient. Stoichiometrically one molecule fumaric acid is combined with two molecules of desloratadine.

The invention provides pharmaceutically elegant and desirable properties needed for a drug to be administered to allergic patients, that has excellent color and thermal stability for solid dosage form and is free of undesired solvating agents such as water and organic solvents.

Related patents include:

- U.S. Patent No. 4,659,716 which discloses descarbonylethoxyloratadine possessing antihistaminic properties with substantially no sedative properties. This U.S. patent also discloses methods of making descarbonylethoxyloratadine, pharmaceutical compositions it and methods of using the compositions to treat allergic reactions in mammals. The compound is taught to form salts with fumaric acid among other pharmaceutically acceptable acids.
- U.S. Patent No: 5,595,997 discloses pharmaceutical compositions and methods for treating allergic rhinitis using descarbonylethoxyloratadine.
- U.S. Patent No. 6,100,274 pharmaceutical compositions containing descarbonylethoxyloratadine.
- PCT WO 99/01450 discloses polymorphs of descarbonylethoxyloratadine and pharmaceutical compositions containing them. The polymorph forms are different from those of this invention. Polymorphs of loratadine are disclosed in U.S. Patent No. 6,335,347.

Detailed Description of the Invention

This invention of polymorphic forms I and II of hemifumarate crystalline form of desloratadine refers to the preparation of hemifumarate salt and two novel polymorphs of the compound. This polymorphic salt formation of desloratadine further enhances the scope of formulation development bioavailability.

The present invention discloses a new method of preparation of polymorphic forms I and II of desloratadine hemifumarate that are more stable in different ranges of pH and more soluble in water and or in protic organic solvents. It has been discovered that specific solvents and experimental conditions which consistently produce two distinctly different crystalline polymorphs of desloratadine hemifumarate thereby allowing commercial production of a stoichiometrically consistent pharmaceutical product having constant physical properties.

During preparation of desloratadine hemifumarate, two sets of conditions are kept constant.

In one case while mixing the ethanolic solution of desloratadine and fumaric acid, the solution state mixing condition can be from about 55°C to 70°C. The solution is stirred at this temperature for 30 to 45 minutes after mixing, and the solid filtration is carried out in hot condition. In this situation, the polymorphic form 2 (differential scanning calorimetry, hereinafter "DSC", 232°C ± 2°) is generated.

In the other set of conditions, the mixing is at 15°C to room temperature (25°C) and is stirred the solution at this temperature for 30 to 45 minutes, then filtered at room temperature. The process and the use of room temperature are preferred to generate the crystalline polymorphic form 1 (DSC of 224°C ± 2°C).

The amounts of the two components of the reaction are employed stoichiometrically, with 2 mols of desloratadine to 1 mol of the fumaric acid.

It has been observed that polymorphic form 1 can be changed to polymorphic form 2 under vacuum at 50°C. However, both the polymorphs are stable and do not change polymorphic form even after crushing in to a solid powder form.

Figures 1 and 2 show the difference of polymorphic form 1 and polymorphic form 2 in FT-IR. A clear distinguishable peaks of form 2 at 1085 cm⁻¹, 875 cm⁻¹, 845 cm⁻¹, 755 cm⁻¹, 745 cm⁻¹, 730 cm⁻¹ and 1277 cm⁻¹ have been observed whereas these peaks are missing in form 1. A comparison of the hygroscopicity of the polymorphic desloratadine hemifumarate salts (forms 1 and 2) of the present invention and the standard desloratadine free base over a range of relative humidity (RH) of 90% have been studied. The results show a good compatibility of hygroscopicity of the two polymorphic forms of hemifumarate salts with desloratadine standard in DVS. Desloratadine hemifumarate polymorphic form 2 and standard desloratadine show very similar moisture absorption value (0.3%) whereas desloratadine polymorphic form 1 exhibit a little higher value (0.9%).

It has been reported that acidic excipients degrade desloratadine at 40°C and 75% RH for one week. Desloratadine standard and the two polymorphic forms (polymorphs 1 and 2) were mixed with three volumes of lactose monohydrate and kept at 40°C and 75% RH for one week, the standard desloratadine showed discoloration whereas two polymorphs retained its crystallinity, color and the texture. This stability study convincingly indicates that polymorphs 1 and 2 are more stable than free base desloratadine under stressed condition. Again, ready conversion of polymorphs 1 to 2 under reduced pressure and temperature identify polymorph 2 as a suitable candidate for solid dosage pharmaceutical composition.

Solubility: Solubility of desloratadine standard and desloratadine hemifumarate polymorphs 1 and 2 were determined photometrically in water, acetate buffer (pH = 5.0) and 0.01N HCl at λ_{\max} 293 nM.

Standard desloratadine: Solubility in H₂O = 0.010 mg/mL, 0.1N HCl = 38.24 mg/mL, acetate buffer (pH = 5.0) = 12.84 mg/mL.

Desloratadine hemifumarate (polymorph 1): Solubility in H₂O = 0.441 mg/mL, 0.1N HCl = 7.45 mg/mL, acetate buffer (pH = 5.0) = 1.76 mg/mL.

Desloratadine hemifumarate (polymorph 2): Solubility in H₂O = 0.553 mg/mL, 0.1N HCl = 7.25 mg/mL, acetate buffer (pH = 5.0) = 1.74 mg/mL.

X-ray powder diffractometry (XRD) study of desloratadine forms 1 and 2 is done in the following manner. The powder of polymorph is filled in an aluminum holder and exposed to CuK α radiation (40 kV x 30 mA) in a wide range XRD (Model D5005, Siemens). The instrument is operated in the step-scan mode, in increments of 0.02° 2 θ . The angular range is 5 to 50° 2 θ and counts are accumulated for 1 second at each step. A typical x-ray diffraction pattern for forms 1 and 2 is as follows, wherein d represents the interplanar spacing and I/I₀ represents the typical relative intensities. In the following table (desloratadine hemifumarate forms 1 and 2) only those peaks are listed whose relative intensity I/I₀ is equal or greater than 10%.

<u>POLYMORPH 1</u>		<u>POLYMORPH 2</u>	
d	I/I ₀	d	I/I ₀
12.32	26	14.14	14
10.53	11	10.74	13
8.444	19	7.158	39
8.149	16	7.084	20
6.550	25	5.983	12
6.281	22	5.663	61
6.185	35	5.365	33
6.034	15	5.257	100
5.553	88	5.064	12
5.373	64	4.973	46
5.096	59	4.809	16
4.960	41	4.745	43
4.745	34	4.477	32
4.470	26	4.449	26
4.403	30	4.399	60
4.365	46	4.317	54
4.159	84	4.012	49
4.124	73	3.772	26
4.061	35	3.745	61
3.750	79	3.722	97
3.716	100	3.590	88
3.659	27	3.561	59
3.589	14	3.385	24
3.398	11	2.986	17
3.362	16	2.949	11
3.277	10	2.836	20
3.090	23	2.778	10
3.051	11	2.616	10
3.003	15	2.481	12
2.784	10		
2.507	12		

Pharmaceutical Compositions

Pharmaceutical compositions of this invention may contain in addition to an anti-allergically effective amount of the polymorph form of descarbonylethoxyloratadine as the active ingredient, inert pharmaceutically acceptable carriers that may be solids or liquids. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegration agents; it can also be an encapsulating material. In powders, the carrier is a

finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5% to about 20% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methycellulose, sodium carboxymethyl-cellulose and a low melting wax, or cocoa butter and the like.

The term "compositions" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, caches are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for topical administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Topical formulation useful for nasal or ophthalmic administration is also contemplated. Topical formulation suitable for nasal administration may be solutions or suspensions. Ophthalmic formulations may be solutions, suspension or ointments. Ointments usually contain lipophilic carriers, such as mineral oil and/or petrolatum. Solution for ophthalmic administration may contain sodium chloride, acid and/or base to adjust the pH as well as purified water and preservatives.

The anti-allergic effective amount of the polymorph form of descarbonylethoxyloratadine for topical administration varies from 0.1% to 5% by weight of the total pharmaceutical composition. The preferred amount varies from 0.5% to 2% by weight of the total pharmaceutical composition.

The anti-allergic effective amount of the polymorph form of descarbonylethoxyloratadine for oral administration varies from about 1-50 mg/day, preferably about 2.5-20 mg/day and more preferably about 5-10 mg/day in single or divided doses. The most preferred amount is 5.0 mg, once a day.

Of course the precise dosage and dosage regimen may be varied depending upon the requirements of the patients (e.g., his or her sex, age) as well as the severity of the allergic condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

The polymorph form of descarbonylethoxyloratadine possesses antihistaminic properties.

The following examples illustrate the preparation of novel polymorphic forms of desloratadine hemifumarate.

Example 1: Preparation of polymorph 1 of descarbonylethoxyloratadine hemifumarate

5.0 g desloratadine is dissolved in 50.0 mL anhydrous ethanol by heating and then allow it to cool to room temperature. The clear solution is cooled by ice water and to it is added 0.875 g anhydrous fumaric acid dissolved in 35.0 mL anhydrous ethanol at room temperature. Addition of ethanolic fumaric acid solution to the cooled ethanolic desloratadine is carried out all at once. After addition the mixture is stirred at cool temperature for 15 minutes and then slowly allowed to come to room temperature and is then stirred at room temperature for 30 minutes. After the stirring the solid is filtered and washed with copious amount of ethanol until the filtrate becomes colorless. The white solid obtained (4.4 g) is first dried in the vacuum pump and then kept in the vacuum oven at room temperature for 2 hours and 30 minutes. DSC shows an endotherm at 224°C.

Example 2: Preparation of polymorph 2 of descarbonylethoxyloratadine hemifumarate

5.0 g desloratadine is dissolved in 50.0 mL anhydrous ethanol by heating and then allow it to boil. The clear hot solution is allowed to stir close to the boiling temperature of ethanol and to it is added hot solution of 0.875 g anhydrous fumaric dissolving in 35.0 mL

anhydrous ethanol. Addition of hot ethanolic fumaric acid solution to the hot ethanolic desloratadine is carried out all at once. After addition the mixture is stirred at this hot condition for 45 minutes. After the stirring the solid is filtered and washed with copious amount of warm ethanol until the filtrate becomes colorless. The white solid obtained (4.0 g) is first dried in the vacuum pump and then kept in the vacuum oven at room temperature for 2 hours and 30 minutes. DSC shows an endotherm at 232°C.

What is claimed is:

1. Polymorph forms 1 and 2 of descarbonylethoxyloratadine hemifumarate having by the following x-ray powder diffraction pattern expressed in terms of "d" spacing and relative intensities ("RI"):

<u>POLYMORPH 1</u>		<u>POLYMORPH 2</u>	
d	I/I ₀	d	I/I ₀
12.32	23	11.14	11
10.53	11	10.74	13
8.444	19	7.158	39
8.149	16	7.084	20
6.550	25	5.983	12
6.281	22	5.663	61
6.185	35	5.365	33
6.084	19	5.267	100
5.553	88	5.064	12
5.373	64	4.973	46
5.096	59	4.809	16
4.960	41	4.745	43
4.745	34	4.477	32
4.470	26	4.449	26
4.403	30	4.399	60
4.365	46	4.317	54
4.159	84	4.012	49
4.124	73	3.772	26
4.061	35	3.745	61
3.750	79	3.722	97
3.716	100	3.590	88
3.659	27	3.561	59
3.589	14	3.385	24
3.398	11	2.986	17
3.362	16	2.949	11
3.277	10	2.836	20
3.090	23	2.778	10
3.051	11	2.616	10
3.003	15	2.481	12
2.784	10		
2.507	12		

2. A pharmaceutical composition comprising an anti-allergic effective amount of the polymorph forms of descarbonylethoxyloratadine hemifumarate of claim 1 and a pharmaceutically acceptable carrier.

3. A pharmaceutical composition comprising an anti-allergic effective amount of the polymorph form 1 descarbonylethoxyloratadine hemifumarate of claim 2 and a pharmaceutically acceptable carrier.
4. A pharmaceutical composition comprising an anti-allergic effective amount of the polymorph form 2 descarbonylethoxyloratadine hemifumarate of claim 2 and a pharmaceutically acceptable carrier.
5. A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of the either of the polymorph forms of descarbonylethoxyloratadine hemifumarate of claim 1.
6. The process of preparing the polymorph forms of descarbonylethoxyloratadine hemifumarate comprising:
 - a) mixing the ethanolic solution of desloratadine and fumaric acid at a temperature of from about 55°C to 70°C, and stirring for 30 to 45 minutes after mixing, and thereafter filtering the solid thereby prepared in hot condition; to yield the polymorphic form 2 having a DSC of 232°C ± 2°C; or
 - b) mixing the ethanolic solution of desloratadine and fumaric acid at a temperature of from about 15°C to room temperature (25°C) and stirring at this temperature for 30 to 45 minutes, then filtering at room temperature; to yield the polymorphic form 1 having a DSC of 224°C ± 2°C.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4545 C07D401/04 //(C07D401/04,221:00,211:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 42290 A (FISCHER JANOS ;FODOR TAMAS (HU); LEVAI SANDOR (HU); PETENYI ENDREN) 30 May 2002 (2002-05-30) page 3, line 5 - line 10; example 5 page 8, line 1 - line 5 ---	1-6
Y	WO 99 01450 A (SCHERING CORP) 14 January 1999 (1999-01-14) cited in the application page 2, paragraph 1; claims; examples 1-3 ---	1-6
Y	EP 0 152 897 A (SCHERING CORP) 28 August 1985 (1985-08-28) page 2, last paragraph --- -/--	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

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28/11/2003

Name and mailing address of the ISA.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/22312

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 659 716 A (VILLANI FRANK J ET AL) 21 April 1987 (1987-04-21) cited in the application column 1, line 47 -column 2, line 5 -----	1-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/22312

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 5 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0242290	A	30-05-2002	HU 0004701 A2	28-11-2002
			AU 1842202 A	03-06-2002
			CA 2425422 A1	30-05-2002
			CZ 20031321 A3	13-08-2003
			EP 1347965 A1	01-10-2003
			WO 0242290 A1	30-05-2002
			NO 20032314 A	18-07-2003
WO 9901450	A	14-01-1999	AT 239010 T	15-05-2003
			AU 734487 B2	14-06-2001
			AU 8271098 A	25-01-1999
			BR 9811658 A	05-09-2000
			CN 1261886 T	02-08-2000
			DE 69814076 D1	05-06-2003
			EP 0993455 A1	19-04-2000
			HU 0004308 A2	28-10-2001
			JP 2002507991 T	12-03-2002
			NO 996547 A	01-03-2000
			NZ 501417 A	27-10-2000
			PL 337712 A1	28-08-2000
			RU 2197485 C2	27-01-2003
			SK 185299 A3	11-07-2000
			TR 9903308 T2	21-11-2000
			WO 9901450 A1	14-01-1999
			ZA 9805783 A	19-01-1999
EP 0152897	A	28-08-1985	AT 47140 T	15-10-1989
			AU 570306 B2	10-03-1988
			AU 3993885 A	10-09-1985
			DE 3573600 D1	16-11-1989
			DK 469485 A ,B,	14-10-1985
			EP 0152897 A1	28-08-1985
			FI 853675 A ,B,	25-09-1985
			HU 38332 A2	28-05-1986
			JP 5072910 B	13-10-1993
			JP 61501205 T	19-06-1986
			LU 90738 A9	09-05-2001
			WO 8503707 A1	29-08-1985
			US 4659716 A	21-04-1987
US 4659716	A	21-04-1987	AT 61364 T	15-03-1991
			AU 638019 B2	17-06-1993
			AU 5702690 A	04-10-1990
			AU 600665 B2	23-08-1990
			AU 5737486 A	18-12-1986
			CA 1272480 A1	07-08-1990
			CA 1307791 C2	22-09-1992
			DE 3677842 D1	11-04-1991
			DK 220986 A	14-11-1986
			EP 0208855 A1	21-01-1987
			ES 8800679 A1	01-02-1988
			FI 861987 A ,B,	14-11-1986
			FI 87648 B	30-10-1992
			HK 75993 A	06-08-1993
			HU 41731 A2	28-05-1987
			IE 59110 B1	12-01-1994
			IL 78771 A	29-11-1990
			IL 91953 A	29-11-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members.

International Application No

PCT/US 03/22312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4659716	A	JP 2511412 B2	26-06-1996
		JP 61289087 A	19-12-1986
		JP 2519880 B2	31-07-1996
		JP 8059657 A	05-03-1996
		KR 9001853 B1	24-03-1990
		PH 25101 A	19-02-1991
		PT 82570 A ,B	01-06-1986
		SG 69193 G	06-08-1993
		AT 47140 T	15-10-1989
		AU 570306 B2	10-03-1988
		AU 3993885 A	10-09-1985
		DE 3573600 D1	16-11-1989
		DK 469485 A ,B,	14-10-1985
		EP 0152897 A1	28-08-1985
		FI 853675 A ,B,	25-09-1985
		HU 38332 A2	28-05-1986
		JP 5072910 B	13-10-1993
		JP 61501205 T	19-06-1986
		LU 90738 A9	09-05-2001
		WO 8503707 A1	29-08-1985